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151. (Once Amended) A system according to claim 150, wherein the particles are of a size of between $1/3 \mu\text{m}$ to $3 \mu\text{m}$, and the ratio is in the range between 10:1 and 1:10.

152. (Once Amended) A system according to claim 150, wherein the particles are of a size of between $3 \mu\text{m}$ to $100 \mu\text{m}$, and the ratio is in the range between 1.4:1 and 1:100.

Remarks

Claims 106-159 remain pending in the application. Claims 142, 151, and 152 have been amended as shown above. The claims were amended to more fully clarify the invention. No new matter has been added by the amendments above. Specifically, support for the amendment to claim 142 related to the $0.4 \mu\text{L}$ volume can be found at least at page 65, line 1 of the application as published. Favorable reconsideration is respectfully requested in light of the above amendments and the following comments.

Claims 151 and 152 are rejected under 35 U.S.C. § 112, second paragraph. Applicants respectfully traverse this rejection.

Claims 142-150, 153, 155-159 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kosaka (U.S. Patent No. 5,457,526). Applicants respectfully traverse this rejection.

Claims 151-152 and 154 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kosaka (U.S. Patent No. 5,457,526). Applicants respectfully traverse this rejection.

Claims 106-141 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Brule et al. (GB 2 152 660 A). Applicants respectfully traverse this rejection.

Rejection under 35 U.S.C. § 112

Claims 151 and 152 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner noted that the phrase "the ratio" lacks antecedent basis.

Claims 151 and 152 have been amended to be dependent on claim 150 instead of claim 142. Applicants respectfully assert that the phrase "the ratio" now has antecedent basis. Applicants therefore respectfully request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 102

Claims 142-150, 153, 155-159 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kosaka (U.S. Patent No. 5,457,526). The Examiner asserts that Kosaka teaches an apparatus for analyzing particles in a liquid sample comprising a sample compartment containing a volume of liquid sample wherein light is transmitted through the sample compartment and is detected by an array of active detection elements wherein the sample compartment has a wall part allowing electromagnetic signals from the sample in the compartment to pass through the wall after passing through a focusing lens and a processor for processing the intensities detected by the detection elements.

Applicants respectfully assert that Kosaka does not teach a device that has a sample compartment volume of at least 0.04 μL . From the disclosure of Kosaka, the volume of the sample utilized can be determined. The sample flow 18 in Kosaka is 10 to 20 μm in width (col. 6, line 5). Assuming a circular sample flow with a diameter of 20 μm , the cross section of the flow is $(0.01 \text{ mm})^2 * \pi$, or 0.0003 mm^2 . It is evident from Kosaka that the height of the volume observed is considerably less than the cross section of sample flow. Assuming that the thickness of the volume observed is even 5 μm , the complete volume observed is 0.0000016 μL . In order to observe 0.04 μL , as Applicants system does, the thicknesses of the observed cross section would have to be 133 mm, which is clearly far beyond the disclosure of Kosaka. Applicants respectfully assert therefore that Kosaka does not anticipate the pending claims because it fails to disclose a sample compartment with a sample of at least 0.04 μL or more.

Applicants furthermore assert that Kosaka does not render the pending claims obvious. Kosaka teaches a volume that is 25,000 times smaller than the volume of claim 142 of Applicants invention. Kosaka have therefore clearly chosen a different approach to assess particles, namely one based on an assessment of extremely small volumes (with corresponding higher magnification). The solution of Applicants' invention is based on assessments of much larger volumes. The teachings of Kosaka can therefore not be

applied to Applicants' invention because modification of Kosaka in such a manner would render it nonfunctional for its purpose.

Rejection under 35 U.S.C. § 103 over Kosaka

Claims 151-152 and 154 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kosaka (U.S. Patent No. 5,457,526). The Examiner reiterates the teachings of Kosaka discussed above with respect to the rejection under 35 U.S.C. § 103 and then admits that Kosaka lacks teachings about the ranges of the ratio and the average thickness of the interior of the compartment. However, the Examiner asserts that, with regard to claim 154, varying the sizes, proportions, etc. is not considered novel, and that it would have been an obvious expedient for one of ordinary skill in the art to reconfigure the thickness of the wall to achieve a more accurate measurement. With respect to claims 151 and 152, the Examiner asserts that it would have been obvious to one of ordinary skill in the art to modify the range of ratios to discover the optimum working conditions.

Applicants respectfully disagree with the Examiner's contentions with regard to obviousness. First of all, as pointed out above, the disclosure of Kosaka cannot be modified to obtain Applicants' invention without making it nonfunctional for its own purpose. However, even if Kosaka could be modified without rendering it nonfunctional, Applicants submit that claims 151, 152, and 154 would still not be obvious.

Although Kosaka does not expressly disclose what ratio is used, the reference does contain enough information to allow estimation of the linear arrangement. The size of the sample flow is 10 to 20 μm . The sample flow is imaged on a linear array 24 via lenses 20 and 22 (Figure 1, col. 6, lines 5-8). Kosaka does not disclose the actual number of detection elements. The size of the detection elements is 20 μm (col 6, lines 63-64, "photodiodes pi being arranged in one lateral row at pitches of scores of micrometers", scores being 20 or a group of 20 things). It is therefore not possible to directly and unambiguously derive the linear arrangement from Kosaka. Figure 2 discloses two areas A1 being a detection area (col 5, line 65) and A2 being an illumination area (col 6, lines 1-2). A1 does not disclose the actual size of the photo sensor array, but only the area of the flow cell from which signals are exposed via lenses 20 and 22 (Figure 1) onto the photo sensor array 24. The ratio between A1 and A2 does not disclose a linear arrangement.

However, from the size of the detection elements and the information available in Figure 9, it is possible to calculate a linear arrangement by assuming that Figure 9 or 10 are not schematic. The detector in Kosaka is a linear array of detection elements. Each detection element in the sensor array detects a signal which is sampled over a period T , which is typically several hundreds of nanoseconds (col. 6, lines 48-50). One particle may for example be sampled 13 times (col. 7, lines 21-24). For each particle, the symbol j denotes the sampling cycle number (col. 6, lines 50-51). As the particle passes the detection area, the pixels provide a signal indicative of the particle. In Figure 9, nine different sampling cycles are shown. In the first sampling cycle (0), none of the pixels detect the presence of a particle. At sampling time (1), a number of pixels detect the presence (hatched area) and others detect the absence of a particle. At sampling cycle (2), more pixels detect the presence. The difference between two sampling cycles correspond to at least one pixel, otherwise no difference would be detected.

Figure 9 indicates a small difference between sampling cycle (3) and sampling cycle (4). The difference in width between the hatched areas of sampling cycles (3) and (4) is less than one mm (left border of the hatched area). Thus the size of one pixel must correspond to less than one mm or less in the Figure. Therefore, the whole detection area must be imaged on more than 120 pixels (width of the detection area in the figure is approximately 12 cm). Standard detection arrays were available at the date of Kosaka that were either 128 or 256 pixels wide, so it can be safely assumed that either 128 or 256 pixels have been used. We know from the text that the width of the sample flow is 10 to 20 μm . Therefore, we can deduce from Figure 2 that the detection area is wider, and probably covers a width of 30 μm . If the array consists of 128 pixels each 20 μm wide, the total width of the array is 2.56 mm. Onto this is exposed an area being 0.03 mm wide. **This corresponds to a linear arrangement of 85:1.** If the size of the pixels is larger or if the array consists of more pixels, then the linear arrangement is much larger.

The presence of a very detailed picture of a particle in Figure 3A strongly indicates a very high linear arrangement. Furthermore, the ratio of the sample flow to the array of detection elements in Figure 1, indicate a very high linear enlargement.

Kosaka teaches a ratio of at least 85:1, which is far from the ratio of less than 10:1 of claim 150. Furthermore, as stated above, Kosaka does not disclose a volume of at

least 0.04 μ L. Consequently, Kosaka lacks several features of the claims. There would have been no motivation to modify Kosaka to create Applicants' invention.

More specifically, the ratios of claims 151 and 152 could not be based on an optimization of Kosaka. Kosaka may have been optimizing the ratio for their own teachings, but the use of such optimums in Applicants' invention would not give optimum values. The ratios of claims 151 and 152 are based on a different technique than Kosaka, namely a technique where a much larger volume (above 0.04 μ L) is assessed at one time using much lower magnification.

With respect to claim 154, Kosaka does not teach the thickness of the interior of the compartment. The thickness of claim 154 is not a mere configuration of Kosaka. As stated above, Kosaka utilizes a very different process and system, and reconfiguring the thickness of Kosaka would not lead to Applicants' invention as defined by claim 154, because the volume would still be lacking.

Based on the above comments, Applicants respectfully assert that Kosaka does not render Applicants' invention obvious at least because there would be no motivation to modify the teachings of Kosaka to obtain Applicants' invention. Applicants respectfully request that this rejection be withdrawn in light of the above comments.

Rejection under 35 U.S.C. § 103 over Brule

Claims 106-141 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Brule et al. (GB 2 152 660 A). The Examiner asserts that Brule teaches a method for analysis of biological products comprising the steps of illuminating a sample compartment containing a volume of liquid sample wherein light is transmitted through the sample compartment and is detected by an array of active detection elements wherein the images are divided into sub area and the sub areas are processed accordingly. The Examiner then asserts that it would have been obvious to obtain the range of the ratios because optimization of ranges is well within one of skill in the art.

Applicants respectfully assert that several of the features claimed in Applicants' invention are neither disclosed nor suggested by Brule. Brule does not disclose a sample compartment. Instead Brule discloses "depositing a succession of samples on a continuous mobile rest, spreading them out in the viewing path of a video system" (claim

1). The succession of samples are effectively drops. Brule therefore does not know the exact volume examined by the video system. In the absence of a sample compartment, Brule is concerned with an entirely different system than is the Applicants' invention.

Brule also does not disclose a ratio. However, it can be deduced that the enlargement is very large. In example 2(page 3, lines 63-72), it is claimed that they can view nuclei and different types of polynuclear constituents inside blood cells. In order to do this, the enlargement must be very large.

Brule also does not disclose the assessment of at least 10 biological particles. As neither the volume nor the concentration of cells nor the dilutions are disclosed in Brule, the number of particles assessed in one volume cannot be deduced from Brule.

Furthermore, Brule does not disclose a repeatability error of 33% at most. On page 3, line 17, it is reported that an error of 5% can be achieved. In order to achieve 5% overall error, it is necessary to identify around 400 objects according to the statistical behavior of counting. When considering the measurement of the number of bacteria in a sample of milk, where the normal level of bacteria in milk is 30,000/mL to 100,000/mL, it becomes evident that a volume of milk, equivalent to more than 4 μ L (prior to staining and dilution) must be analyzed in order to count at least 400 objects. Clearly, Brule does not disclose assessment of such a large volume at one time.

Taking the requirement of the magnification into account, it becomes evident that the level of error reported relates to the accuracy in the identification of each object, rather than the accuracy in the estimate of the number of objects present in the sample.


Applicants respectfully assert that one of skill in the art would not have been able to modify the teachings of Brule to obtain Applicants' invention because Brule simply lacks features to modify. Therefore, Brule does not render Applicants' invention obvious.

Conclusion

In view of the amendments and comments presented herein, favorable reconsideration in the form of a Notice of Allowance is respectfully requested.

Respectfully submitted,
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Marked up version of Claims

In the Claims

Please amend claims 142, 151, and 152 as follows.

142. (Once Amended) A system for the assessment of at least one parameter of a species of biological particles in a liquid analyte material, comprising:

a sample compartment for containing a volume of a liquid sample representing the analyte material and comprising a plurality of particles, or a plurality of particles isolated from a volume of liquid sample representing the analyte material, from which sample compartment electromagnetic signals from the sample in the compartment can pass to the exterior, the size of the volume being [1] 0.04 μl or more[.];

an array of active detection elements arranged such that electromagnetic signals from said volume having passed from the compartment is detected on the detection elements forming an image of the plurality of particles[.]; and

a processor for processing the intensities detected by the detection elements.

151. (Once Amended) A system according to claim [142] 150, wherein the particles are of a size of between $1/3 \mu\text{m}$ to $3 \mu\text{m}$, and the ratio is in the range between 10:1 and 1:10.

152. (Once Amended) A system according to claim [142] 150, wherein the particles are of a size of between $3 \mu\text{m}$ to $100 \mu\text{m}$, and the ratio is in the range between 1.4:1 and 1:100.